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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,886	GIBBS ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-38* is/are rejected.

7)☒ Claim(s) *33-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 33-38 are pending and under consideration in this Office Action.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The specification is objected to because Figure 1 which illustrates a nucleotide sequence has not been identified with a specific SEQ ID NO. Appropriate correction is requested.

3. Claims 33-38 are objected to because of the following informalities: the claims recite the abbreviations "NP", "S-2238", and "AT-III" without defining the abbreviations in the claims. For examination purposes, it is assumed that "NP" stands for "novel polypeptide" as stated on page 5, line 15 of the specification; and "AT-III" stands for antithrombin IIII as stated on page 4, line 13.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 33-38 recite "NP' which is vague and indefinite. The metes and bounds of the claim are unclear since it is not certain if it actually stands for a novel polypeptide. This phrase is an opinion of the applicant on the merits of the claim and is therefore considered improper. It is suggested that "NP" be deleted.

Additionally, claims 33-38 do not provide a SEQ ID NO for the "NP" and the "reference sequence thrombin". Without a SEQ ID NO it would be impossible to do a meaningful search let alone a search for polypeptides that are 80% homologous by amino acid sequence to thrombin.

Claim 38 recites "... R233A NP, E229D NP, E229F NP..." which is vague and indefinite. The metes and bounds of the claim are unclear since it is not certain if applicants are actually

claiming a specific polypeptide of a specific SEQ ID NO with specific amino acid substitutions or if applicants are claiming any other proteolytically active polypeptide with an amino acid sequence that is different from SEQ ID NO: 2.

For examination purposes, the claim is assumed to encompass any proteolytically active polypeptide of any amino acid sequence, which has a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of any reference thrombin.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the evaluation of the claims for compliance with the written description requirement of 35 U.S.C. 112, of particular relevance is 66 FR 1099, Friday, January 5, 2001,which states:

> "*Eli Lilly* explains that a chemical compound's name does not necessarily convey a written description of the named chemical compound, particularly when a genus of compounds is claimed. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1405. The name, if it does no more than distinguish the claimed genus from all others by function, does not satisfy the written description requirement because "it does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. Thus *Eli Lilly* identified a set of circumstances in which the words of the claim did not, without more, adequately convey to others that applicants had possession of what they

claimed." (see p. 1100, 1st column, line 47 to 2nd column, line 2).

The claims are drawn to a method for treating a genus of thrombotic diseases or conditions comprising the use of a genus of proteolytically active polypeptides that have at least 80% amino acid homology to the amino acid sequence of any thrombin (including mutants and variants thereof) and has a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of the reference sequence thrombin.

The scope of the genus of thrombotic diseases encompasses many diseases or conditions and include stroke, coronary heart disease, neonatal purpura fulminans, cardiac bypass surgery, thrombosis, atherothrombosis, and thromboembolism. The genus of thrombotic diseases is highly variable because of widely differing etiologies, symptoms, and treatments for each of the diseases or conditions. The scope of the genus of proteolytically active polypeptides used in the method includes many polypeptides with widely differing structural, chemical, and physiochemical properties including widely differing amino acid sequences. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

While the specification discloses in Example 4 that the polypeptide designated as E229A consisting of the amino acid sequence of SEQ ID NO: 2 where aspartate at position 229 is replaced with alanine and the polypeptide designated as K52A consisting of the amino acid sequence of SEQ ID NO: 2 where lysine at position 52 is replaced with alanine were able to prolong the clotting time in healthy cynomolgus monkeys; the recitation of the name "proteolytically active NP" and its desired properties does not define any structural features and amino acid sequences commonly possessed by the genus of proteolytically active polypeptides. The specification does not describe and define any structural features and amino acid sequences commonly possessed by the genus. The specification does not describe that any "proteolytically active NP" was used to treat any thrombotic disease or condition including cardiac bypass surgery.

Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus of proteolytically active polypeptides for use in the claimed method nor recognize that the specification provides a description for any method for treating any thrombotic diseases or condition using the genus of proteolytically active polypeptides.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definitions, such as the structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v, Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe the genus of

genetic materials, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g. structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. Therefore, the instant claims are not adequately described.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of a genus of proteolytically active polypeptides and any method for treating a genus of any thrombotic diseases or conditions comprising the use of said genus of proteolytically active polypeptides.

8. Claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature and breadth of the claims encompass a method for treating any thrombotic diseases or conditions comprising the use of any proteolytically active polypeptide that has at least 80% amino acid homology to the amino acid sequence of any thrombin (including mutants and variants thereof), and has a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of the reference sequence thrombin. Furthermore, thrombotic diseases encompasses many diseases or conditions and include stroke, coronary heart disease, cardiac bypass surgery, neonatal purpura fulminans, thrombosis, atherothrombosis, and thromboembolism.

In regard to atherothrombosis, Viles-Gonzalez et al. (Eur Heart J. 2004 Jul;25(14):1197-207) teach that although antithrombotic therapy using various agents including anticoagulants is safe and efficient, the morbidity and mortality due to atherothrombosis is still unacceptably high (see entire publication especially Table 5 and **Conclusions** section on p.1204). Thus, it cannot be predicted that administering the claimed proteolytically active polypeptide can be useful in treating atherothrombosis. While the specification discloses in Example 4 the polypeptide designated as E229A consisting of the amino acid sequence of SEQ ID NO: 2 where aspartate at position 229 is replaced with alanine and the polypeptide designated as K52A consisting of the amino acid sequence of SEQ ID NO: 2 where lysine at position 52 is replaced with alanine were able to prolong the clotting time in healthy cynomolgus monkeys, the specification does not provide any *in vivo* working examples showing that the claimed proteolytically active polypeptide is able to

treat any human patient having atherothrombosis. Furthermore, the specification does not provide any *in vivo* working examples showing that the claimed proteolytically active polypeptide is able to treat any other thrombotic diseases or conditions including stroke, coronary heart disease, cardiac bypass surgery, and thromboembolism.

Therefore, in view of the unpredictability in the art, the lack of *in vivo* working examples, and the lack of further guidance in how to use the claimed proteolytically active polypeptide to actually treat any thrombotic disease or condition, it would require an undue amount of experimentation to use the claimed inventions.

Furthermore, the claims lack enablement on the following additional grounds. While the claims are enabled for making specific variants of SEQ ID NO: 2 such as K52A and E229A, they are not enabled for making any polypeptide that are simply 80% homologous to any thrombin. The claims encompass proteolytically active polypeptides that have an amino acid sequence that is 80% homologous to the amino acid sequence of any thrombin including mutants and variants thereof. While the specification discloses several mutants of thrombin consisting of SEQ ID NO: 2 having a single, specific amino acid substitution with alanine, aspartate, phenylalanine, serine, tryptophan, tyrosine, arginine, cysteine, or lysine, the specification does not provide guidance, prediction, and working examples for making any proteolytically active polypeptides that have an amino acid sequence that is 80% homologous to the amino acid sequence of any thrombin including mutants and variants thereof.

Thus, an undue amount of trial and error experimentation must be preformed to search and screen for any polypeptide that has 80% homology to any reference thrombin which has protease activity and has a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of the reference thrombin. Such experimentation entails searching for any reference thrombin, mutating any amino acid residue in the reference thrombin (e.g. amino acid substitution, deletion, insertion, and combinations thereof) to make a polypeptide that has 80% identity to the reference thrombin, and searching and screening for polypeptides that have proteolytic activity and a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of the reference sequence thrombin. General teaching regarding screening and searching for the claimed invention using the assays stated in the specification is not guidance for making the claimed invention. Therefore, such trial and error experimentation to make the claimed proteolytically active polypeptides is undue and well outside the realm of routine experimentation.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 33-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffen et al. (WO 93/09807, published 05/27/1993).

Griffen et al. teaches and contemplates methods for treating thrombosis comprising administration of therapeutically effective amount of a plasma derived or recombinant thrombin mutants including thrombins E192Q, K52E, and active site acylated thrombin (see entire publication especially beginning on p. 30, section **Therapeutic or diagnostic composition**; and pp. 67-72 describing administration of mutant thrombin K52E)

The teachings of Griffen et al. anticipate the claims since thrombin mutants E192Q and K52E, which have a single amino acid substitution, have at least 80% amino acid homology to the wild-type thrombin, and these mutants were used in treating thrombosis which is a condition where a blood clot forms in a vein or artery and is encompassed by the recited phrase "thrombotic diseases or conditions".

Since the thrombin mutants E192Q and K52E, which have a single amino acid substitution, have at least 80% amino acid homology to the wild-type thrombin, then the examiner takes the position that it would inherently have has a ratio of protein C activating activity to fibrinogen clotting activity that is greater than about twice that of the wild-type thrombin, inherently possess greater than twice the activity of the wild-type thrombin when measured by hydrolysis of S-2238 in the presence of heparin-dependent AT-III inhibition, inherently is devoid of detectable fibrinogen clotting activity, and inherently retains at least 5% of wild-type thrombin protein C activating activity.

Since the Patent Office does not have the facilities for examining and comparing the claimed proteolytically active polypeptide to the thrombin mutants E192Q and K52E taught by Griffen et al., the burden is on applicant to show that the prior art thrombin mutants E192Q and K52E are different from the claimed proteolytically active polypeptide. See *In re Best*, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Claim 35 is also included in this rejection since no patentable weight is given to the preamble of the recited method for treating thrombotic disease arising from cardiac bypass

surgery since it merely recites the purpose of the method. Because the process steps of the method of Griffen et al. are the same as the process step of claim 35, then the method of Griffen et al. would inherently treat thrombotic disease arising from cardiac bypass surgery.

In regard to claim 38, as stated above in the rejection of the claim under 35 U.S.C. 112, second paragraph, the claim is assumed to encompass any proteolytically active polypeptide of any amino acid sequence. Thus, claim 38 is also anticipated by the teachings of Griffen et al. since the claim is not limited to any particular polypeptide of a specific amino acid sequence.

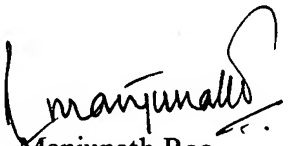
Thus, the reference teachings anticipate the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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